

FORM PTO-1390 (Modified) (REV 11-98)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				PU3514USW	
				U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR <b>09/787327</b> )	
INTERNATIONAL APPLICATION NO. <b>PCT/EP99/06886</b>		INTERNATIONAL FILING DATE <b>17 September 1999</b>		PRIORITY DATE CLAIMED <b>18 September 1998</b>	
TITLE OF INVENTION <b>ANTIVIRAL COMBINATIONS</b>					
APPLICANT(S) FOR DO/EO/US <b>BROWN, Nathaniel A.; CONDREAY, Lynn, D.; GRAY, Douglas, Fraser; RUBIN, Marc</b>					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
<ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371 (c) (2)) <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</li> <li>7. <input checked="" type="checkbox"/> A copy of the International Search Report (PCT/ISA/210).</li> <li>8. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)) <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau)</li> <li>b. <input checked="" type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li>9. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>10. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). <b>Condreay and Rubin</b></li> <li>11. <input checked="" type="checkbox"/> A copy of the International Preliminary Examination Report (PCT/IPEA/409).</li> <li>12. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).</li> </ol>					
Items 13 to 20 below concern document(s) or information included:					
<ol style="list-style-type: none"> <li>13. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>14. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>15. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</li> <li>16. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>17. <input type="checkbox"/> A substitute specification.</li> <li>18. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>19. <input checked="" type="checkbox"/> Certificate of Mailing by Express Mail.</li> <li>20. <input checked="" type="checkbox"/> Other items or information:</li> </ol>					
<div style="border: 1px solid black; padding: 5px;"> <p>Copy of Form PCT/RO/101</p> <p>Copy of PCT Publication Cover Sheet</p> </div>					

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR <b>09/787327</b> )		INTERNATIONAL APPLICATION NO. PCT/EP99/06886		ATTORNEY'S DOCKET NUMBER PU3514USW	
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21. The following fees are submitted

BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5) ) :	CALCULATIONS	PTO USE ONLY																																																																	
<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1,000.00																																																																			
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Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	<b>\$860.00</b>																																																																		
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<table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:15%;">CLAIMS</th> <th style="width:20%;">NUMBER FILED</th> <th style="width:20%;">NUMBER EXTRA</th> <th style="width:15%;">RATE</th> <th style="width:30%;"></th> </tr> </thead> <tbody> <tr> <td>Total claims</td> <td>15 - 20 =</td> <td>0</td> <td>x \$18.00</td> <td style="text-align: right;"><b>\$0.00</b></td> </tr> <tr> <td>Independent claims</td> <td>4 - 3 =</td> <td>1</td> <td>x \$80.00</td> <td style="text-align: right;"><b>\$80.00</b></td> </tr> <tr> <td colspan="4">Multiple Dependent Claims (check if applicable) <input type="checkbox"/></td> <td style="text-align: right;"><b>\$0.00</b></td> </tr> <tr> <td colspan="4" style="text-align: center;"><b>TOTAL OF ABOVE CALCULATIONS =</b></td> <td style="text-align: right;"><b>\$940.00</b></td> </tr> <tr> <td colspan="4">Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable) <input type="checkbox"/></td> <td style="text-align: right;"><b>\$0.00</b></td> </tr> <tr> <td colspan="4" style="text-align: center;"><b>SUBTOTAL =</b></td> <td style="text-align: right;"><b>\$940.00</b></td> </tr> <tr> <td colspan="4">Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f))</td> <td style="text-align: right;"><b>\$0.00</b></td> </tr> <tr> <td colspan="4" style="text-align: center;"><b>TOTAL NATIONAL FEE =</b></td> <td style="text-align: right;"><b>\$940.00</b></td> </tr> <tr> <td colspan="4">Fee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable) <input type="checkbox"/></td> <td style="text-align: right;"><b>\$0.00</b></td> </tr> <tr> <td colspan="4" style="text-align: center;"><b>TOTAL FEES ENCLOSED =</b></td> <td style="text-align: right;"><b>\$940.00</b></td> </tr> <tr> <td colspan="4"></td> <td style="text-align: right;">Amount to be: refunded \$</td> </tr> <tr> <td colspan="4"></td> <td style="text-align: right;">charged \$</td> </tr> </tbody> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		Total claims	15 - 20 =	0	x \$18.00	<b>\$0.00</b>	Independent claims	4 - 3 =	1	x \$80.00	<b>\$80.00</b>	Multiple Dependent Claims (check if applicable) <input type="checkbox"/>				<b>\$0.00</b>	<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$940.00</b>	Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable) <input type="checkbox"/>				<b>\$0.00</b>	<b>SUBTOTAL =</b>				<b>\$940.00</b>	Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f))				<b>\$0.00</b>	<b>TOTAL NATIONAL FEE =</b>				<b>\$940.00</b>	Fee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable) <input type="checkbox"/>				<b>\$0.00</b>	<b>TOTAL FEES ENCLOSED =</b>				<b>\$940.00</b>					Amount to be: refunded \$					charged \$		
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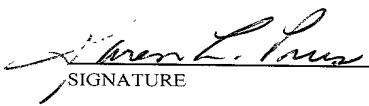
☐ A check in the amount of \_\_\_\_\_ to cover the above fees is enclosed.

☒ Please charge my Deposit Account No **07-1392** in the amount of **\$940.00** to cover the above fees  
A duplicate copy of this sheet is enclosed

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No **07-1392** A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

David J. Levy Glaxo Wellcome Inc. Global Intellectual Property Dept. Five Moore Drive, PO Box 13398 Research Triangle Park, NC 27709 Telephone: 919-483-2370 Fax: 919-483-7988	<div style="text-align: center;">             SIGNATURE         </div> <div> <b>Karen L. Prus</b>            NAME  <b>39,337</b>            REGISTRATION NUMBER  <b>March 14, 2001</b>            DATE         </div>
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532 Rec'd PCT/PTO 16 MAR 2001

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Nathaniel A. BROWN et al  
International Application No.: PCT/EP99/06886  
International Filing Date: 17 September 1999  
Title: ANTIVIRAL COMBINATIONS

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Commissioner of Patents  
Washington, D.C. 20231

## FIRST PRELIMINARY AMENDMENT

Dear Sir:

The above identified application is being transmitted herewith for entry in the US National Phase under Chapter II of the PCT for the purpose of adding the priority information. Please amend the application as follows:

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b)

In the Specification:

On the first line of the specification, after the Title, please add:

--This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. **PCT/EP99/06886** filed **17 September 1999**, which claims priority from **GB9820420.9** filed **18 September 1998**.--

In the Claims:

Please delete Claim 11 and Claims 16-21.

Please amend the Claims as follows:

### Clean Copy of Amended Claims

Claim 1 (Amended in IPER) A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

Claim 3 (Amended here and in IPER) A combination according to claim 1 for use in medicine.

Claim 4 (Amended here and in IPER) A pharmaceutical formulation comprising a combination according to claim 1 in association with one or more pharmaceutically acceptable carriers therefor.

Claim 5 (Amended in IPER) A pharmaceutical formulation for use in the treatment of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[R]-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 6 (Amended here and IPER) A formulation according to claim 4 in unit dosage form.

Claim 7 (Amended here and IPER) A formulation according to claim 4 suitable for oral administration.

Claim 8 (Amended) A formulation according to claim 5 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

Claim 9 A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

Claim 10 A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

Delete Claim 11

Claim 12 (Amended) A method according to claim 10 wherein the combination is administered simultaneously.

Claim 13 (Amended) A method according to claim 10 wherein the combination is administered sequentially.

Claim 14 (Amended) A method according to claim 10 wherein the combination is administered as a single combined formulation.

Claim 15 (Amended) A method as claimed in claim 10 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus.

Delete Claims 16-21

Claim 22 (Amended in IPER) A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

11/02/2010 12:28:50

## REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information. The claims have been amended to place them in form appropriate to US practice and to reduce the filing fee by removing multiple dependency. Claims 1, 3, 4, and 5 have been amended to parallel the amended claims as indicated in the PCT International Preliminary Examination Report. Claims 11 and 16-21 have been deleted. It is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted;

Date: March 14, 2001

By: Karen L. Prus  
Karen L. PRUS  
Attorney of Record, Reg. No 39,337

Glaxo Wellcome Inc.  
Global Intellectual Property Department  
Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709-3398  
Telephone: 919-483-3323  
Fax: 919-483-7988

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## ANTIVIRAL COMBINATIONS

### Abstract

The present invention relates to therapeutic combinations comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one (lamivudine) and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine, (PMEA or adefovir) and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine, (the oral prodrug of PMEA, adefovir dipivoxil) which have anti-hepatitis B virus (HBV) activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors.

Pub. No. 2002/024660

## Version With Markings to Show Changes Made to Claims

Claim 1 (Amended in IPER) A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent [selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and] bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

Claim 2 A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

Claim 3 (Amended here and in IPER) A combination according to [any one of] claim[s] 1 [or 3] for use in medicine.

Claim 4 (Amended here and in IPER) A pharmaceutical formulation comprising a combination according to [any one of] claim[s] 1 [to 3] in association with one or more pharmaceutically acceptable carriers therefor.

Claim 5 (Amended in IPER) A pharmaceutical formulation for use in the treatment of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

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Claim 6. (Amended here and in IPER) A formulation according to claim[s] 4 [or 5] in unit dosage form.

Claim 7. (Amended here and in IPER) A formulation according to [any one of] claim[s] 5 [to 6] suitable for oral administration.

Claim 8. (Amended) A formulation according to [any one of] claim[s] 5 [to 7] comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

Claim 9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

Claim 10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

Claim 11 (Deleted)

Claim 12. (Amended) A method according to claim 10 [or claim 11] wherein the combination is administered simultaneously.

Claim 13. (Amended) A method according to claim 10 [or claim 11] wherein the combination is administered sequentially.

Claim 14. (Amended) A method according to claim 10 [or claim 11] wherein the combination is administered as a single combined formulation.

002240 22/2/60

Claim 16 (Deleted)

Claim 18 (Deleted)

Claim 20 (Deleted)

Claim 22. (Amended in IPER) A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

09/787 327

Antiviral Combinations

5 The present invention relates to therapeutic combinations comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one (lamivudine) and  
a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine, (PMEA or adefovir) and  
10 bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine, [the oral prodrug of PMEA, adefovir dipivoxil]. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HBV infections including infections with HBV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus.

15 Hepatitis B is a viral disease transmitted orally or parentally by contaminated material such as blood or blood products, contaminated needles, sexually, and vertically from infected or carrier mothers to their off-spring. In those areas of the world where the disease is common, vertical transmission at an early age results in a high proportion of infected individuals becoming chronic carriers of hepatitis B. An estimated 350 million people world-wide are chronically infected with hepatitis B and as many as 150 million may die from liver disease in the absence of intervention.

25 Currently, the only established approach to treatment of hepatitis B is repeated injections of interferon, which may be associated with unpleasant side effects, and produces a long lasting response in only one third or less of those treated. Interferon is an immune modulator designed to boost the disease fighting ability of the immune system.

30 Lamivudine has been reported to be effective against HBV in a two year study, showing that most patients showed substantially reduced levels of viral replication with 52% maintaining undetectable levels of virus thorough to the end of the second year.

Adefovir has been reported to possess anti-HBV activity in vitro, and the oral prodrug of adefovir, adefovir dipivoxil, has been shown to be active against HBV replication in vivo and is currently in phase II clinical studies with patients who have chronic hepatitis B viral infection.

There has been a report that there is lack of cross-resistance to PMEA for Human hepatitis B DNA polymerase which expresses lamivudine codons, X. *Xiong et al. (Hepatology Vol 26, No. 4, Pt. 2, 1997, Abstract No. 1211).*

The use of combinations of the invention may give rise to equivalent antiviral effect with reduced toxicity, or an increase in drug efficacy because synergy between compounds occurs. Lower overall drug doses will also possibly reduce the frequency of occurrence of drug resistant variants of HBV.

We have now found that lamivudine exhibits unexpected advantages when used in combination with adefovir. In particular the combinations shows a statistically significant synergistic anti-HBV effect. Early results have shown that the combination of lamivudine and adefovir dipivoxil also exhibits a synergistic anti-HBV-effect. It is a feature of this invention that the use of these drug combinations will provide synergistic antiviral effects, more complete viral suppression, viral suppression over longer periods, limit the emergence of drug resistant HBV mutants and allow better management of drug related toxicities. The use of these drug combinations may also result in a decrease of the number of, for example, tablets administered a day, therefore may increase patient compliance.

As will be appreciated by those skilled in the art, references herein to treatment extend to prophylaxis as well as to the treatment of established infections and symptoms.

Pharmaceutically acceptable salts of lamivudine, adefovir, or adefovir dipivoxil include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene- p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic,

malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and  $\text{NR}_{4+}$  (where R is  $\text{C}_{1-4}$  alkyl) salts.

Preferred esters of lamivudine, adefovir or adefovir dipivoxil are independently selected from the following group: (1) carboxylic acid esters in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, *n*-propyl, *t*-butyl, or *n*-butyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen,  $\text{C}_{1-4}$  alkyl, or  $\text{C}_{1-4}$  alkoxy), or amino; (2) sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); and (4) phosphonate esters. In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a physiologically acceptable salt thereof.

Particularly preferred esters are the mono-, di-, and triphosphate esters of lamivudine (which may be optionally blocked), or any other compound which upon administration to a human subject is capable of providing (directly or indirectly) said mono-, di-, or triphosphate ester.

Thus according to one aspect, the present invention provides a combination comprising (2*R*,*cis*)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second

therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

5

Preferably the second therapeutic agent is bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

10

Combinations as described above may herein after be referred to as combinations according to the invention.

15

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester, of lamivudine, adefovir or adefovir dipivoxil or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof.

20

The present invention further provides combinations according to the invention for use in therapy, particularly in the treatment of an HBV infection including infections resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus.

25

According to another aspect, the present invention provides a method for the treatment of a mammal, including a human, suffering from an HBV infection comprising administration of a therapeutically effective amount of a combination according to the invention.

30

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical composition, or sequentially. If there is sequential administration, the delay in administering the second active ingredient should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. It will also be understood that lamivudine, and adefovir dipivoxil, or the pharmaceutically acceptable derivatives thereof or adefovir or the

35

pharmaceutically acceptable derivatives thereof, whether presented simultaneously or sequentially, may be administered individually or in any combination thereof. Lamivudine, and adefovir dipivoxil or adefovir are preferably administered simultaneously or sequentially in separate pharmaceutical formulations, most preferably simultaneously.

Preferably the combination according to the invention is administered as a single combined formulation.

The present invention also provides the use of lamivudine in the manufacture of a medicament for administration simultaneously or sequentially with adefovir or adefovir dipivoxil for the treatment of HBV infections. It will be appreciated that lamivudine, adefovir dipivoxil, or adefovir or any combination thereof (excluding adefovir and adefovir dipivoxil), may be used in the manufacture of the above medicament.

A further aspect of the invention is a combination according to the invention wherein the lamivudine and adefovir dipivoxil or adefovir are present in a synergistic ratio.

The synergistic effects of the combination of lamivudine and adefovir dipivoxil or adefovir or pharmaceutically acceptable derivatives thereof are seen over a ratio, for example, of 40:1 to 1:1 (by weight), preferably 25:1 to 15: 1 (by weight).

Conveniently each compound will be employed in the combination in an amount at which it exhibits anti-HBV activity when used alone.

The amount of a combination of lamivudine, adefovir or adefovir dipivoxil required to be effective as an anti-HBV agent will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

In general for lamivudine a suitable daily dose will be in the range of from about 0.1 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.5 to 20 mg per kilogram body weight per day, most preferably in the range of 0.5 to 2 mg per kilogram body weight per day.

The compound is conveniently administered at a level of about 100 mg per day.

For adefovir dipivoxil a suitable daily dose will be in the range of from about 0.01 to about 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.01 to 1 mg per kilogram body weight per day, most preferably in the range of 0.01 to 0.05 mg per kilogram body weight per day.

Conveniently adefovir dipivoxil is administered at a level of about 10 mg per day.

For adefovir, a suitable daily dose will be in the range of from about 0.01 to about 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.01 to 1 mg per kilogram body weight per day, most preferably in the range of 0.01 to 0.05 mg per kilogram body weight per day.

Conveniently adefovir is administered at a level of about 10 mg per day.

Unless otherwise indicated all weights of active ingredients are calculated in terms of the drug per se. In the case of a pharmaceutically acceptable derivatives of lamivudine, adefovir dipivoxil or adefovir, or a solvate of any thereof the figures would be increased proportionately. The desired dose is preferably presented as two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing from 1 to 1500 mg, preferably from 5 to 1000 mg, most preferably from 5 to 500 mg of active ingredient per unit dosage form. Alternatively, if the condition of the recipient so requires, the dose may be administered as a continuous infusion.



The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

5 While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical composition. Pharmaceutical compositions according to the present invention comprise a combination according to the invention in  
10 association with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical composition. The references hereinafter to compositions refer  
15 unless otherwise stated to compositions containing either the combination or a component thereof.

A combination of lamivudine and adefovir dipivoxil or adefovir or pharmaceutically acceptable derivatives thereof may conveniently be presented  
20 as a pharmaceutical composition with one or more pharmaceutically acceptable carrier thereof in a unitary dosage form. A convenient unitary dosage formulation contains the active ingredients in amounts of from 1 mg to 2 g each, for example, 2 mg to 200 mg such as 25 to 150 mg of lamivudine and 5 to 60 mg of adefovir or adefovir dipivoxil.

25 Pharmaceutical compositions may also be prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk  
30 supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physicians instructions.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patients packs of each composition, within a package insert diverting the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention there is provided a patient pack comprising at least one active ingredient of the combination according to the invention and an information insert containing directions on the use of the combination of the invention.

According to another aspect the invention provides a double pack comprising in association for separate administration lamivudine and adefovir dipivoxil or adefovir or pharmaceutically acceptable derivatives thereof.

Compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in

5 a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

15 Preferably the combinations according to the invention are administered orally.

20 Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

25 Topical administration may also be by means of a transdermal iontophoretic device.

30 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

35 Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active

combination with the softened or melted carrier(s) followed by chilling and shaping in moulds.

5 Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the  
10 compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and  
15 suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as herein before recited, or an appropriate  
20 fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those  
25 suitable for oral administration may include such further agents as sweeteners, thickeners and flavouring agents.

The compounds of the combination of the present invention may be obtained in a conventional manner.

30 Methods for the preparation of lamivudine are described in International Patent Applications Numbers. WO91/17159, and WO 95/29174 incorporated herein by reference.

Methods for the preparation of adefovir are described in European Patent No. 206459, incorporated herein by reference.

5 Methods for the preparation of adefovir dipivoxil are described in European Patent No. 481214 incorporated herein by reference.

10 The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes lamivudine, adefovir dipivoxil or adefovir or multiples thereof or a physiologically functional derivative of any of the aforementioned compounds.

Example 1: Tablet Formulation

15 The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Formulation A

	<u>mg/tablet</u>
Active Ingredient A	100
Active Ingredient B	30
Lactose B.P.	105
Povidone B.P.	7
Sodium Starch Glycollate	10
Magnesium Stearate	3
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	255

Formulation B

	<u>mg/tablet</u>
Active Ingredient A	100

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Active Ingredient B	30
Lactose B.P.	75
Avicel PH 101	30
Povidone B.P.	7
Sodium Starch Glycollate	10
Magnesium Stearate	3
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	255

Formulation C

	<u>mg/tablet</u>
Active Ingredient A	100
Active Ingredient B	5
Lactose B.P.	100
Starch	25
Povidone	2
Magnesium Stearate	2
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	234

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The following formulations, D and E, are prepared by direct compression of the admixed ingredients. The lactose in formulation E is of the direct compression type (Dairy Crest - "Zeparox").

Formulation D

	<u>mg/tablet</u>
Active Ingredient A	100
Active Ingredient B	30
Pregelatinized Starch NF15	75
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	205

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Formulation E

	<u>mg/tablet</u>
Active Ingredient A	100
Active Ingredient B	5
Lactose B.P.	70
Avicel	50
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Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the ingredients with a solution of povidone followed by the addition of magnesium stearate and compression.

	<u>mg/tablet</u>
Active Ingredient A	100
Active Ingredient B	30
Hydroxypropylmethylcellulose (Methocel K4M Premium)	28
Lactose B.P.	13
Povidone B.P.	7
Magnesium Stearate	2
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	180

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

Example 2: Capsule FormulationsFormulation A

A capsule formulation is prepared by admixing the ingredients of formulation D in Example 1 above and filling into a two-part hard gelatin capsule. Formulation B (infra) is prepared in a similar manner.

## Formulation B

	<u>mg/capsule</u>
Active Ingredient A	100
Active Ingredient B	5
Lactose B.P.	70
Sodium Starch Glycollate	10
Magnesium Stearate	1
	<hr/>
	186

## Formulation C

	<u>mg/capsule</u>
Active Ingredient A	100
Active Ingredient B	30
Macrogel 4000 B.P.	170
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	300

5 Capsules of formulation C are prepared by melting the Macrogel 4000 B.P., dispersing the active ingredient in the melt and filling the melt into a two-part hard gelatin capsule.

## Formulation D

	<u>mg/capsule</u>
Active Ingredient A	100
Active Ingredient B	5
Lecithin	50
Arachis Oil	50
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	205



Capsules of formulation D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

### 5 Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients a, b, and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

	<u>mg/capsule</u>
(a) Active Ingredient A	100
Active Ingredient B	30
(b) Microcrystalline Cellulose	60
(c) Lactose B.P.	60
(d) Ethyl Cellulose	6
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	256

### Example 3: Injectable Formulation

#### Formulation A

	<u>mg</u>
Active Ingredient A	100
Active Ingredient B	5
Hydrochloric Acid Solution 0.1 M <u>or</u>	
Sodium Hydroxide Solution 0.1 M q.s. to pH	4.0 to 7.0
Sterile water q.s. to	10 ml

The active ingredient is dissolved in most of the water (35°-40°C) and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or the sodium

hydroxide as appropriate. The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures and overseals.

5

Formulation B

Active Ingredient A	125 mg
Sterile, Pyrogen-free, pH 7 Phosphate Buffer, q. s. to	25 ml

Example 4: Intramuscular injection

Active Ingredient A	100 mg
Active Ingredient B	30 mg
Benzyl Alcohol	0.067 g
Glycofurol 75	0.94 g
Water for injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml amber glass vials (type 1).

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Example 5: Syrup

Active Ingredient A	100 mg
Active Ingredient B	5 mg
Sorbitol Solution	0.6 g
Glycerol	0.85 g
Sodium Benzoate	0.0025 g
Flavour, Peach 17.42.3169	0.0125 ml
Purified Water q.s. to	5.00 ml

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbital solution and finally the flavour. The volume is made up with purified water and mixed well.

#### Example 6: Suppository

	<u>mg/capsule suppository</u>
Active Ingredient A	100
Active Ingredient B	30
Hard Fat, B.P. (Witepsol H15 - Dynamit Nobel)	1770
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	1900

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200µm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250µm stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.02 g of the mixture is filled into suitable, 2 ml plastic moulds. The suppositories are allowed to cool to room temperature.

#### Example 7: Pessaries

	<u>mg/pessary</u>
Active Ingredient A	100
Active Ingredient B	5
Anhydrate Dextrose	160
Potato Starch	150
Magnesium Stearate	3
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	418

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

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## Biological Data

Example 8.

5 The human hepatoblastoma cell line (Hep-G2-2.2.15) which constitutively produces infectious HBV was seeded into 96 well microtiter plates at a density of  $5 \times 10^3$  cells per well. These cells were treated with a combination of lamivudine and PMEA on triplicate plates. Culture media containing drugs was replenished every other day for 9 days, at which time supernatants were collected and  
10 analyzed for HBV content.

The lamivudine/PMEA combination was tested twice in triplicate in matrix fashion. Experiment 1 utilised a lamivudine range of 100 nM to 0.14 nM (3-fold dilutions in columns), and PMEA, 9-[(R)-2-(phosphonomethoxy)ethyl]adenine (adefovir), at concentrations of 1  $\mu$ M to 10 nM (3.16 fold dilutions in rows).  
15 Experiment 2 was performed with dilutions of Lamivudine ranging from 100nM to .045 nM (in 3-fold dilutions in columns), and a PMEA range of 5  $\mu$ M to 0.16 nM (3.16 fold dilutions in rows). Both drugs were diluted in a separate 96 well microtiter plate, and subsequently transferred onto plates containing the cell monolayers. Cells are grown in 150  $\mu$ l RPMI 1640 supplemented with 2 mM L-Glutamine and 10% fetal bovine serum. Prior to transfer of drug, 120  $\mu$ l of media was removed from the cells, leaving 30  $\mu$ l on the monolayers to prevent drying. 90  $\mu$ l of fresh media without drug was added, followed by the addition of 30  $\mu$ l of 5X drug dilutions. Lamivudine and PMEA were each tested on their respective plates individually at the same concentrations. Data were normalised to values  
20 obtained with non-drug treated cells, and expressed as a percent of control for analysis.

The method used for detection of HBV has been previously described (*Jansen RW, Johnson LC, Averett, DR. High-Capacity in vitro assessment of anti-hepatitis B virus compound selectivity by a virion-specific polymerase chain reaction assay. Antimicrob Agents Chem 1993; 37 (3): 441-447.*). Briefly, HBV detection was performed by "capturing" virus from supernatants on Anti-HBsAg coated plates, washing, denaturing to release HBV DNA, performing PCR with biotinylated primers, streptavidin capture of biotinylated PCR products with concomitant probe hybridization, addition of substrate, and reading optical  
25 densities of the colorimetric reaction. Dilutions of a standardized HBV-containing  
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supernatant were included on every plate, and HBV DNA concentrations of test wells were calculated from this HBV standard curve. The useful range of detection is at least .045 to 45 fg of HBV DNA, where 30 copies of the genome can be reliably detected. Samples were tested in conjunction with both positive (.448 fg/ul plasmid DNA) and negative (RPMI medium supplemented with 2 mM L-Glutamine and 10% Fetal calf serum) controls.

The average IC<sub>50</sub> and standard error of the IC<sub>50</sub>s for the triplicate plates were calculated using SAS nonlinear regression to fit data to the Hill equation for each concentration response curve. When only a single determination of an IC<sub>50</sub> for a particular dose combination could be made, the average of the standard errors from adjacent concentrations was used to estimate the standard error. Fractional inhibitory concentrations (FIC<sub>50</sub>) were calculated for each combination and plotted using the isobologram representation (*Berenbaum, M.C. (1985) The Expected Effect of a Combination of Agents: the General Solution. J. Theor. Biol. 114, 413-431*). To assess statistical significance of synergy or antagonism, an unpaired t-test was used to compare each sum of paired FIC<sub>50</sub> values with the theoretical value of 1. P values less than 0.05 were considered statistically significant. Comparison of P values between experiments must be interpreted with great care, as the experiments utilized different test concentration ranges (or ranges useable by the isobologram method). In some cases not all concentrations tested could support calculation of an IC<sub>50</sub>, since response was inhibited to a greater extent than 50 percent of control for all doses.

Figure 1 shows a single isobologram, produced by combining the data from both experiments, showing a statistically significant synergism.

### Example 9

The IC<sub>50</sub> for PME A was determined against wild type (WT) and lamivudine resistant HBV transiently expressed in a cell culture system as described below. HepG2 cells were transiently transfected with plasmid containing the HBV genome that had the wild type sequence or contained the following lamivudine resistant mutations in the reverse transcriptase gene; M552I, M552V, L528M, L528MM552V. It was previously determined that only the M552I and L528MM552V mutations were observed in HBV infected patients that developed

resistance to lamivudine therapy although the individual M552V and L528M mutations partially contributed to the loss in sensitivity of lamivudine against HBV replication *in vitro* (Allen MI, Deslauriers M, Andrews CW, Tipples GA, Walters KA, Tyrrell DLJ, Brown N for the Lamivudine Clinical Investigation Group, and Condearey LD. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. HEPATOLOGY 1998; 27:1670-1677).

HepG2 cells were seeded into 96-well Costar plates at 6300 cells per well in 150 µl of HepG2 media (Dulbecco's Modified Eagle Medium (DMEM), containing 10% fetal bovine serum) and were incubated overnight at 37°C. For each transfected well, 75 ng of plasmid DNA and 0.5 µl of lipofectamine (Gibco) were incubated together for 30 minutes at room temperature in 12.5 µl of OptiMem (Gibco) prior to addition of DNA/lipofectamine mixture to cells. Each well was rinsed with 150 µl of unsupplemented DMEM. The DNA/lipofectamine mixture was added to each well in a total volume of 150 µl of OptiMem media. The cells were incubated with the DNA/lipofectamine solution for 5 hours at 37°C. After incubation, 150 µl of DMEM containing 20% serum was added to each well and plates were incubated overnight at 37°C. The media was replaced with 150 µl of HepG2 media only or media containing PMEA.

2.2.15 cells were seeded into 96-well Costar plates at 2250 cells per well in 150 µl of complete media (RPMI media containing 10% fetal bovine serum) and were incubated overnight at 37°C. The media was replaced with 150 µl of complete media only or media containing the desired concentration of PMEA.

Transfected cells, as well as 2.2.15 stable HBV-producer cells, were treated with control drug-free media or media containing PMEA every other day (day 1, 3, and 5). Final concentrations of PMEA for cell treatment were used at 25, 5, 1, 0.2, 0.04 µM (for WT plasmid transfected cultures and control 2.2.15 cells) or 125, 25, 5, 1, 0.2 µM (for all mutant plasmid transfected cultures).

HBV DNA levels were quantitated from media harvested from cells on day 7 using the methods described in Jansen RW, Johnson LC, Averett, DR. High-Capacity *in vitro* assessment of anti-hepatitis B virus compound selectivity by a virion-specific polymerase chain reaction assay. Antimicrob Agents Chem 1993; 37 (3): 441-447. Further details are given in Example 8.

Cytotoxicity due to drug treatment was determined using the DNA stain Bisbenzimidazole (H33342 3HCl 4H<sub>2</sub>O; Calbiochem Company, La Jolla CA). After the media was harvested, the cells were fixed with 70% ethanol for 30 minutes.

Cells were rinsed once with serum-free media and incubated with the DNA stain Bisbenzimidazole (H33342 3HCl 4H<sub>2</sub>O; Calbiochem Corporation, La Jolla CA) at 33 µg/ml for 1 hour at 37°C in serum-free medium. Fluorescent values per well were determined with a Millipore Cytofluor 2350 fluorescent plate reader (excitation, 355 nm; emission, 460 nm; arbitrary units). CC<sub>50</sub> values of each compound (concentration of compound that is cytotoxic for 50% of cells) were determined from the percent toxicity of each concentration of compound compared to untreated (no drug) cells using the method described below.

Concentration response curves generated from each construct in the transient transfection experiment were fit to the Hill equation ( $y = V_{max} * (1 - (x^n / (k^n + x^n)))$ ) using non-linear regression to estimate the IC<sub>50</sub> (concentration of drug which inhibited HBV DNA production by 50%, compared to parallel drug-free cultures) and CC<sub>50</sub> of PMEA. The calculated IC<sub>50</sub> for each construct is shown with the 95% confidence bounds for the geometric means for n replicates. The program JMP (SAS, Cary NC) was used to perform student t-test evaluation of the data for determining statistically significant differences between treatment groups. The IC<sub>50</sub> of PMEA obtained against WT HBV produced by the 2.2.15 cells (0.43 µM) was also comparable to the IC<sub>50</sub> value (0.7 µM) using the same cell line. (Heijntink RA, De Wilde GA, Kruining J, Berk L, Balzarini J, De Clercq E, Holy A, Schalam SW. Inhibitory Effect of 9-(phosphonylmethoxyethyl)-adenine(PMEA) on Human and Duck Hepatitis B Virus Infection. *Antiviral Research* 1993; 21 (2): 141-153).

**Table 1.** Comparison of IC<sub>50</sub>s of PMEA between WT HBV and HBV containing lamivudine resistant associated mutations *in vitro*.

HBV construct	IC <sub>50</sub> PMEA (95%CI)	x-fold change in IC <sub>50</sub>
2.2.15	0.43 µM (0.3 - 0.7 µM)	-
WT	0.53 µM (0.34 - 0.8 µM)	-
L528M/ M552V	1.3 µM (0.4 - 4.3 µM)*	2.5
M552I	7.5 µM (1.8 - 32 µM)*	14
M552V	9.8 µM (3.1 - 31 µM)**	18
L528M	0.87 µM (0.4 - 2.0 µM)	1.6



\* Statistically different  $IC_{50}$ s of compound between mutant HBV and WT HBV,  $p < 0.05$ .

+  $IC_{50}$ s are statistically different from each other,  $p < 0.05$ .

- 5 For HepG2 cells, the cytotoxic  $IC_{50}$  for PMPA was greater than 125  $\mu M$ , the cytotoxic  $IC_{50}$  for PMEA varied between 25 to 40  $\mu M$ .

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# Claims

1. A combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

2. A combination according to claim 1 wherein the ratio is in the range 25:1 to 15:1 by weight of active ingredients.

3. A combination according to any one of claims 1 to 3 for use in medicine.

4. A pharmaceutical formulation comprising a combination according to any one of claims 1 to 3 in association with one or more pharmaceutically acceptable carriers therefor.

5. A pharmaceutical formulation for use in the treatment of HBV comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight.

6. A formulation according to claims 4 or 5 in unit dosage form.

7. A formulation according to any one of claims 4 to 6 suitable for oral administration.

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8. A formulation according to any one of claims 5 to 7 comprising between 25 to 150 mg of lamivudine and 5 to 60 mg adefovir dipivoxil.

9. A formulation according to claim 8 comprising 100 mg of lamivudine and 10 mg adefovir dipivoxil.

10. A method for the treatment of a mammal, including a human, with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

11. A method as claimed in claim 10 wherein the combination is as claimed in any of claims 1 to 3.

12. A method according to claim 10 or claim 11 wherein the combination is administered simultaneously.

13. A method according to claim 10 or claim 11 wherein the combination is administered sequentially.

14. A method according to claim 10 or claim 11 wherein the combination is administered as a single combined formulation.

15. A method as claimed in any one of claims 10 to 14 for the treatment of an HBV infection resistant to nucleoside and/or non-nucleoside inhibitors of the replication of the hepatitis B virus

16. Use of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one in the manufacture of a medicament for administration either simultaneously or sequentially with bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine, for the treatment of an HBV infection.

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17. Use of bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine in the manufacture of a medicament for administration either simultaneously or sequentially with (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one for the treatment of an HBV infection.

18. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof for the treatment of an HBV infection.

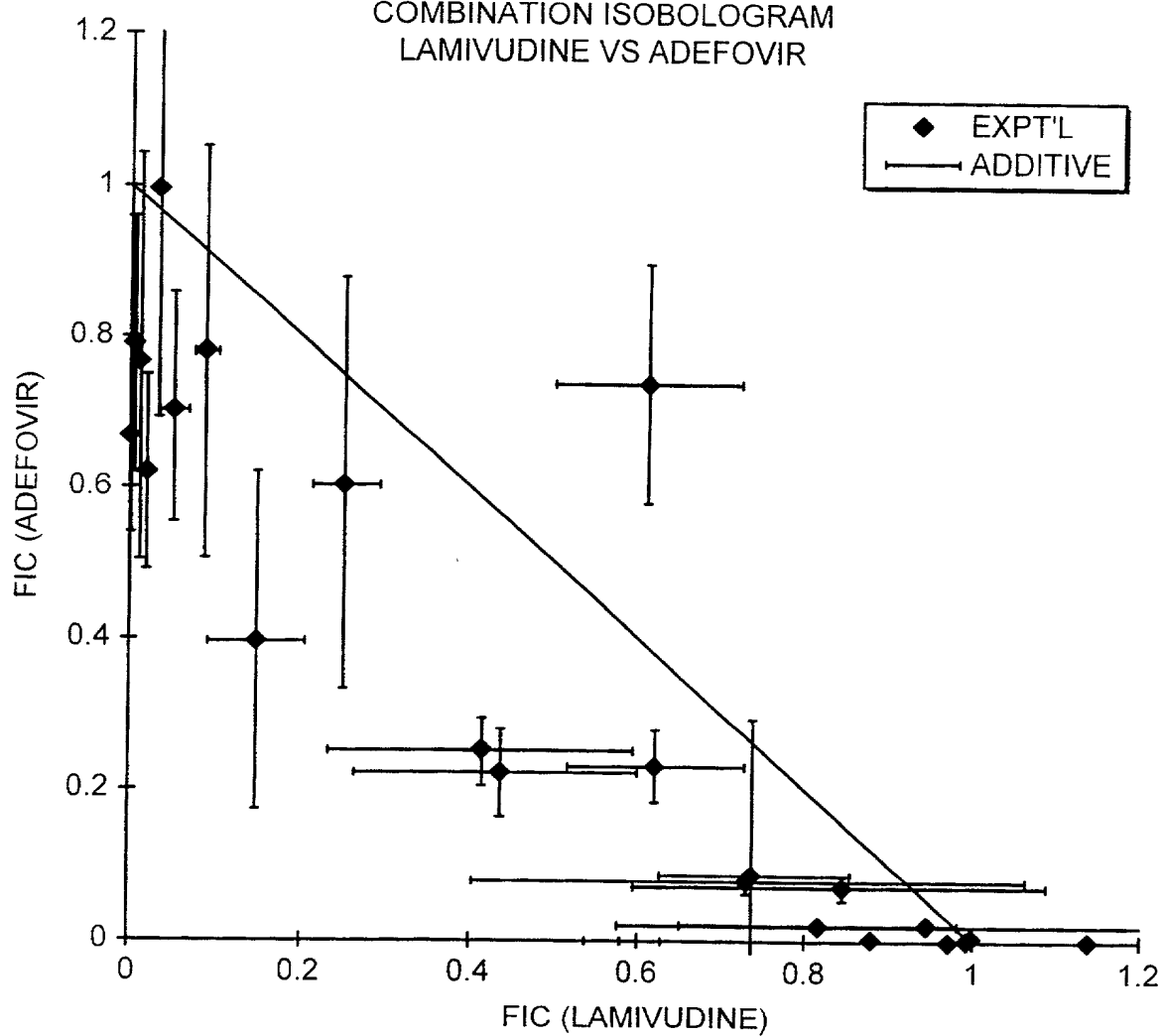
19. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection.

20. Use of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from either (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, or bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof wherein (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and the second therapeutic agent are present in the range 40:1 to 1:1 by weight, for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor.

21. Use of a combination as claimed in any one of claims 1 to 3 for the treatment of an HBV infection resistant to nucleoside and/or nonnucleoside inhibitor of the replication of the hepatitis B virus.

22. A patient pack comprising of at least one active ingredient selected from (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one, and bis(pivaloyloxymethyl)(9-[2-(phosphonomethoxy)ethyl]adenine and an information insert containing directions on the use of both active ingredients together in combination.

FIG. 1

COMBINATION ISOBOLOGRAM  
LAMIVUDINE VS ADEFOVIR

NET SUM	-3.102370207	SE	1.29895894
t	-2.388351257		
AV DEV	-0.141016828		
P (DEV)	0.013449974		

**COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY**ATTORNEY'S DOCKET  
PU3514USWFirst Names Inventor.  
BROWN, Nathaniel A.Complete if known:  
App No.:

Filing Date

Group Art Unit:

(X) Declaration submitted with initial filing or

( ) Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ANTIVIRAL COMBINATIONS**

the specification of which (check only one item below):

[ ] is attached hereto.

OR

[ x ] was filed on 17 September 1999 as United States application Serial No. \_\_\_\_\_ or PCT InternationalApplication Number PCT/EP99/06886 filed and was amended on (MM/DD/YYYY) \_\_\_\_\_ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

**PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:**

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY)	PRIORITY CLAIMED
1. 9820420.9	GB	09/18 /1998	X
2.			
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
1.		
2.		
3.		
4.		
5.		

## DECLARATION FOR "371" APPLICATION

**COMBINED DECLARATION FOR UTILITY or DESIGN  
PATENT APPLICATION WITH POWER OF ATTORNEY** ContinuedATTORNEY'S DOCKET NUMBER  
PU3514USW

2	FULL NAME OF INVENTOR	FAMILY NAME <b>RUBIN</b>	FIRST GIVEN NAME <b>Marc</b>	SECOND GIVEN NAME/INITIAL
0	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY <b>Chapel Hill</b>	STATE OR FOREIGN COUNTRY <b>NC</b>	COUNTRY OF CITIZENSHIP <b>US</b>
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS <b>Glaxo Wellcome Inc. Five Moore Drive, PO Box 13398</b>	CITY <b>Research Triangle Park</b>	STATE & ZIP CODE/COUNTRY <b>NC 27709, US</b>

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## DECLARATION FOR "371" APPLICATION

**COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT  
APPLICATION WITH POWER OF ATTORNEY**ATTORNEY'S DOCKET  
PU3514USWFirst Names Inventor:  
BROWN, Nathaniel A.Complete if known:  
App No.:

Filing Date

Group Art Unit:

(X) Declaration submitted with initial filing or

( ) Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ANTIVIRAL COMBINATIONS**

the specification of which (check only one item below):

[ ] is attached hereto.

OR

[ x ] was filed on 17 September 1999 as United States application Serial No. \_\_\_\_\_ or PCT InternationalApplication Number PCT/EP99/06886 filed and was amended on (MM/DD/YYYY) \_\_\_\_\_ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

**PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:**

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY)	PRIORITY CLAIMED
1. 9820420.9	GB	09/18 /1998	X
2.			
3.			
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5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)
1.	
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**COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY**ATTORNEY'S DOCKET  
PU3514USWFirst Names Inventor:  
BROWN, Nathaniel A.**Complete if known:**  
App No.:

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**ANTIVIRAL COMBINATIONS**

the specification of which (check only one item below):

☐ is attached hereto.

OR

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**COMBINED DECLARATION FOR UTILITY or DESIGN  
PATENT APPLICATION WITH POWER OF ATTORNEY** Continued

 ATTORNEY'S DOCKET NUMBER  
 PU3514USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application.

**PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION**

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one)		
		PATENTED	PENDING	ABANDONED

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith (List name and registration number)

David J. Levy	Reg. No. 27,655	James P. Rick	Reg. No. 39,009	Bonnie L. Deppenbrock	Reg. No. 28,209
Charles E. Dadswell	Reg. No. 35,851	Virginia C. Bennett	Reg. No. 37,092	John L. Lemanowicz	Reg. No. 37,380
Karen L. Prus	Reg. No. 39,337	Frank P. Grassler	Reg. No. 31,164		
Robert H. Brink	Reg. No. 36,094	Christopher P. Rogers	Reg. No. 36,334		
Elizabeth Selby	Reg. No. 38,298	Lorrie Ann Morgan	Reg. No. 38,181		

**Send Correspondence to:**

David J. Levy, Patent Counsel  
 Global Intellectual Property Department  
 Glaxo Wellcome Inc.  
 Five Moore Drive, PO Box 13398  
 Research Triangle Park, NC 27709



23347  
 PATENT TRADEMARK OFFICE

**Direct Telephone Calls to:**

Karen L. Prus  
 919-483-2192

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	<b>BROWN</b>	<b>Nathaniel</b>	<b>A.</b>
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	Cambridge	MA	US
2	INVENTOR'S SIGNATURE	Glaxo Wellcome Inc.	Research Triangle Park	NC 27709, US
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	Five Moore Drive, PO Box 13398	NC	US
	INVENTOR'S SIGNATURE	<b>CONDREAY</b>	<b>Lynn</b>	<b>D.</b>
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	Raleigh	NC	US
	INVENTOR'S SIGNATURE	Glaxo Wellcome Inc.	Research Triangle Park	NC 27709, US
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
2	POST OFFICE ADDRESS	Five Moore Drive, PO Box 13398	NC	US
	INVENTOR'S SIGNATURE	<b>GRAY</b>	<b>Douglas</b>	<b>Fraser</b>
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	Greenford	GB	GB
3	INVENTOR'S SIGNATURE	Glaxo Wellcome plc	Greenford	Middlesex UB6 0HE, GB
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	891-995, Greenford Road	GB	GB
	INVENTOR'S SIGNATURE			

<b>COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY</b> Continued				ATTORNEY'S DOCKET NUMBER <b>PU3514USW</b>
2	FULL NAME OF INVENTOR	FAMILY NAME <b>RUBIN</b>	FIRST GIVEN NAME <b>Marc</b>	SECOND GIVEN NAME/INITIAL
0	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY <b>Chapel Hill</b>	STATE OR FOREIGN COUNTRY <b>NC</b>	COUNTRY OF CITIZENSHIP <b>US</b>
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS <b>Glaxo Wellcome Inc. Five Moore Drive, PO Box 13398</b>	CITY <b>Research Triangle Park</b>	STATE & ZIP CODE/COUNTRY <b>NC 27709, US</b>

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**COMBINED DECLARATION FOR UTILITY or DESIGN  
PATENT APPLICATION WITH POWER OF ATTORNEY** ContinuedATTORNEY'S DOCKET NUMBER  
PU3514USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION**

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one)		
		PATENTED	PENDING	ABANDONED

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Charles E. Dadswell	Reg. No. <u>35,851</u>	Virginia C. Bennett	Reg. No. <u>37,092</u>	John L. Lemanowicz	Reg. No. <u>37,380</u>
Karen L. Prus	Reg. No. <u>39,337</u>	Frank P. Grassler	Reg. No. <u>31,164</u>		
Robert H. Brink	Reg. No. <u>36,094</u>	Christopher P. Rogers	Reg. No. <u>36,334</u>		
Elizabeth Selby	Reg. No. <u>38,298</u>	Lorie Ann Morgan	Reg. No. <u>38,181</u>		

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	INVENTOR'S SIGNATURE			
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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

## DECLARATION FOR "371" APPLICATION

**COMBINED DECLARATION FOR UTILITY or DESIGN  
PATENT APPLICATION WITH POWER OF ATTORNEY** ContinuedATTORNEY'S DOCKET NUMBER  
PU3514USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material\* to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION**

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one)		
		PATENTED	PENDING	ABANDONED

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith. (List name and registration number)

David J. Levy Reg. No. 27,655  
Charles E. Dadswell Reg. No. 35,851  
Karen L. Prus Reg. No. 39,337  
Robert H. Brink Reg. No. 36,094  
Elizabeth Selby Reg. No. 38,298

James P. Riek Reg. No. 39,009  
Virginia C. Bennett Reg. No. 37,092  
Frank P. Grassler Reg. No. 31,164  
Christopher P. Rogers Reg. No. 36,334  
Lorie Ann Morgan Reg. No. 38,181

Bonnie L. Deppenbrock Reg. No. 28,209  
John L. Lemanowicz Reg. No. 37,380

Send Correspondence to:

David J. Levy, Patent Counsel  
Global Intellectual Property Department  
Glaxo Wellcome Inc.  
Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709



23347


PATENT TRADEMARK OFFICE

Direct Telephone Calls to:

Karen L. Prus  
919-483-2192

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2 0 1	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE		Nathaniel	A.
	RESIDENCE & CITIZENSHIP	CITY Cambridge	STATE OR FOREIGN COUNTRY MA	COUNTRY OF CITIZENSHIP US
	POST OFFICE ADDRESS	POST OFFICE ADDRESS Glaxo Wellcome Inc. Five Moore Drive, PO Box 13398	CITY Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709, US
2 0 2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	CONDREAY	Lynn	D.
	RESIDENCE & CITIZENSHIP	CITY Raleigh	STATE OR FOREIGN COUNTRY NC	COUNTRY OF CITIZENSHIP US
	POST OFFICE ADDRESS	POST OFFICE ADDRESS Glaxo Wellcome Inc. Five Moore Drive, PO Box 13398	CITY Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709, US
2 0 3	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	GRAY	Douglas	Fraser
	RESIDENCE & CITIZENSHIP	CITY Greenford	STATE OR FOREIGN COUNTRY GB GBX	COUNTRY OF CITIZENSHIP GB
	POST OFFICE ADDRESS	POST OFFICE ADDRESS Glaxo Wellcome plc 891-995, Greenford Road	CITY Greenford	STATE & ZIP CODE/COUNTRY Middlesex UB6 0HE, GB

<b>COMBINED DECLARATION FOR UTILITY or DESIGN</b>				<b>ATTORNEY'S DOCKET NUMBER</b> PU3514USW	
<b>PATENT APPLICATION WITH POWER OF ATTORNEY</b>				continued	
2	FULL NAME OF INVENTOR	FAMILY NAME <b>RUBIN</b>	FIRST GIVEN NAME <b>Marc</b>	SECOND GIVEN NAME/INITIAL	
0	INVENTOR'S SIGNATURE				3/13/01
0	RESIDENCE & CITIZENSHIP	CITY <b>Chapel Hill</b>	STATE OR FOREIGN COUNTRY <b>NC</b>	COUNTRY OF CITIZENSHIP <b>US</b>	
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS <b>Glaxo Wellcome Inc. Five Moore Drive, PO Box 13398</b>	CITY <b>Research Triangle Park</b>	STATE & ZIP CODE/COUNTRY <b>NC 27709, US</b>	